Medical Policy Reference Manual
Medical Policy

7.01.030 Therapeutic Apheresis

Original MPC Approval: 04/01/1998
Last Review: 09/16/2019
Last Revision: 01/01/2023

Description

Therapeutic apheresis is a procedure in which plasma or cellular components of blood are separated from the circulating blood volume for the treatment of disease. Plasmapheresis, plasma exchange, cytapheresis, and extracorporeal immunoadsorption are all types of apheresis.

Plasmapheresis is a procedure in which plasma is separated from its cellular components. These cellular components are returned to the donor. The plasma may be treated and returned to the donor or discarded and replaced. Therapeutic plasmapheresis is often used in conjunction with immunosuppressives, chemotherapeutic agents and/or corticosteroids to treat disease.

Plasma exchange is a term often used interchangeably with plasmapheresis. During plasma exchange, a large volume of plasma is removed and replaced with either donor plasma or another volume substitute (such as saline, donor serum albumin, fresh frozen plasma). Antibodies, immune complexes, paraproteins, drugs, toxins, inflammatory mediators, and other plasma components may be removed with this technique.

Cytapheresis is the selective removal of red blood cells, white blood cells or platelets. This procedure includes thrombocytapheresis or plateletpheresis (removal of platelets), erythrocytapheresis (removal of erythrocytes) and leukapheresis (removal of leukocytes). The plasma may be returned to the donor or replaced.

Extracorporeal immunoadsorption is a therapeutic apheresis procedure that uses a filter to selectively remove certain components from the plasma, which is treated and returned to the donor. One type of this selective removal is called Protein A Immunoadsorption. Protein A is a molecule present on the cell wall of certain strains of *Staphylococcus aureus*. This protein has an affinity for immunoglobulin G (IgG). The Protein A Immunoadsorption Column is a type of filter that contains a highly purified Protein A bound to a silica matrix. Plasma is separated from the donor's whole blood and is passed through the Protein A Column. Circulating IgG is thereby removed from the plasma. The treated plasma is returned to the donor.

Policy

Therapeutic apheresis is considered **medically necessary** for any of the conditions listed below:

- ABO incompatible hematopoietic progenitor cell transplantation;
- acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome; severity grade 1-2 within 2 weeks of onset; severity grade 3-5 within 4 weeks of onset) (grade 1 = minor symptoms or signs of neuropathy but capable of manual work, grade 2 = able to walk without support but incapable of manual work, grade 3 = ability to walk with assistance, grade 4 = confinement to a bed or chair bound, grade 5 = requiring assisted ventilation for at least part of the day or night);
- ANCA-associated vasculitis (example Wegener's granulomatosis) with associated renal failure (serum Cr > 5.8 mg/dl);
- anti-glomerular basement membrane disease (progressive renal failure due to anti-basement membrane antibodies) (Goodpasture's syndrome);
- chronic inflammatory demyelinating polyneuropathy (CIDP);
- familial homozygous hypercholesterolemia;

- HELLP syndrome of pregnancy (hemolysis, elevated liver enzymes, low platelets);
- hemolytic uremic syndrome (HUS);
- hyperviscosity syndromes associated with Waldenstrom's macroglobulinemia, cryoglobulinemia, multiple myeloma, catastrophic phospholipid syndrome or other conditions;
- idiopathic thrombocytopenic purpura (ITP) in life-threatening situations;
- leukemia;
- multiple sclerosis or other conditions, such as transverse myelitis, acute fulminant central nervous system (CNS) demyelination;
- myasthenia gravis in crisis or as part of preoperative preparation;
- N-methyl-D-aspartate receptor antibody encephalitis;
- paraproteinemia polyneuropathy, IgA or IgG;
- post-transfusion purpura;
- Progressive multifocal leukoencephalopathy associated with natalizumab;
- pure red cell aplasia unresponsive to steroid and immunosuppressive therapy (including sickle cell disease/sickle cell anemia);
- rheumatoid arthritis
- solid organ transplant patients in acute antibody-mediated organ rejection or in those at high risk for antibody-mediated organ rejection;
- thrombotic thrombocytopenic purpura (TTP).

Other applications of therapeutic apheresis for conditions not listed in the above policy statement are considered **experimental / investigational** as they do not meet TEC criteria **#** 2-5. This includes but is not limited to:

- amyotrophic lateral sclerosis (ALS);
- asthma;
- chronic fatigue syndrome;
- multiple sclerosis in the absence of acute fulminant onset;
- paraneoplastic syndromes including Lambert-Eaton myasthenic syndrome;
- paraproteinemic peripheral neuropathy, associated with POEMS syndrome (polyneuropathy, organomegaly, monoclonal protein, and skin hyperpigmentation) and MGUS (monoclonal gammopathy of undetermined significance) or other conditions;
- pemphigus;
- polymyositis and dermatomyositis;
- Refsum's disease (phytanic acid storage disease);
- regional enteritis (Crohn's disease);
- scleroderma;
- systemic lupus erythematosus (SLE).

Policy Guidelines

Experimental/Investigational

The term "experimental/investigational" describes services or supplies that are in the developmental stage and are in the process of human or animal testing. Services or supplies that do not meet all 5 of the criteria listed below adopted by the BlueCross BlueShield Association Technology Evaluation Center (TEC) are deemed to be experimental/investigational:

1. The technology* must have final approval from the appropriate U.S. government regulatory bodies; and
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes; and
3. The technology must improve the net health outcome; and
4. The technology must be as beneficial as any established alternatives; and
5. The improvement must be attainable outside the investigational settings.

* Technology includes drugs, devices, processes, systems, or techniques

Rationale:
The use of therapeutic apheresis is an established treatment for certain indications as outlined in the above policy statement. There is a scarcity of current peer-reviewed literature to support the use of therapeutic apheresis for other than those medically necessary indications.

Update 2019:
A search of peer-reviewed literature was performed for the period of July 2017 through July 2019. The policy statement was updated to include N-methyl-D-aspartate receptor antibody encephalitis and progressive multifocal leukoencephalopathy associated with natalizumab as medically necessary indications.

Update 2017:
A search of peer-reviewed literature was performed for the period June 2015 through June 2017. Findings in the recent literature do not support the use of therapeutic apheresis for other than the medically necessary indications noted in the existing Policy statement.

Update 2015:
A search of peer-reviewed literature was performed for the period of January 2013 through May 2015. There is a scarcity of current peer-reviewed literature to support the use of therapeutic apheresis for other than the medically necessary indications noted in the existing Policy Statement.

Update 2013:
A search of peer-reviewed literature was performed for the period of January 2011 through December 2012. There is a scarcity of current peer-reviewed literature to support the use of therapeutic apheresis for other than those medically necessary indications.

Update 2010:
A search of peer-reviewed literature was performed for the period of December 2008 through December 2010. The policy indications were updated by adding ABO incompatible hematopoietic progenitor cell transplantation and ANCA-associated vasculitis. Medically necessary indications for Guillain-Barré and myasthenia gravis were clarified.

Update 2008:
A search of the peer-reviewed literature was performed, and the reference list updated through November 2008. In the policy indications, IgA, or IgG paraproteinemia polyneuropathy was added to medically necessary indications and Lambert-Eaton myasthenic syndrome was changed to investigational.

Benefit Applications
There are no Benefit Application guidelines for this Medical Policy.

Provider Guidelines
There are no Provider Guidelines for this Medical Policy.

Cross References to Related Policies and Procedures

2.03.005	Adoptive Immunotherapy, Policy
3.01.018	Treatment of PANS / PANDAS, Policy
7.03.001	Human Organ Transplants, Policy
7.03.003	High Dose Chemotherapy / Radiation Therapy with Allogeneic Stem Cell Support, Policy
7.03.004	Placental and Umbilical Cord Blood as a Source of Stem Cells, Policy

References
The following were among the resources reviewed and considered in developing this policy. By reviewing and considering the resources, CareFirst does not in any way endorse the contents thereof nor assume any liability or responsibility in connection therewith. The opinions and conclusions of the authors of these resources are their own and may or may not be in agreement with those of CareFirst.

Adams, D.M., Schultz, W.H., Ware, R.E., & Kinney, T.R. (1996). Erythrocytapheresis can reduce iron overload and prevent the need for chelation therapy in chronically transfused pediatric patients. *Journal of Pediatric Hematologic Oncology, 18, 46-50.*

American Academy of Neurology (1996). Assessment of Plasmapheresis Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 47, 840-3.

American Academy of Neurology. AAN Summary of Evidence-based Guideline for Clinicians-Update: Plasmapheresis in Neurologic Disorders. (2011). Retrieved December 28, 2012, from the World Wide Web at: www.aan.com

American Academy of Neurology. (1991). Task force report of the ad hoc subcommittee of the American Academy of Neurology AIDS task force. *Neurology, 41,* 617-618.

American Academy of Neurology. (1996). Assessment of plasmapheresis. *Neurology, 47,* 840-843.

Anthem BlueCross BlueShield Midwest. (1998, September 1). Therapeutic apheresis, therapeutic phlebotomy. (Medical Policy 11). Mason: Author.

Berkow, R. (Ed.). (1999). *Merck manual* (17th ed.) [On-line]. Available: http://www.merck.com/pubs/mmanual/section11/chapter129/129g.htm

BlueCross and BlueShield of Massachusetts. (1999, May). Plasmapheresis (Medical Policy No. 71). Boston: Author.

Boada, M., Anaya, F., Ortiz, P., Olazarán, J., Shua-Haim, J.R., Obisesan, T.O., … Paetz, A. (2017) Efficacy and safety of plasma exchange with 5% albumin to modify cerebrospinal fluid and plasma amyloid-â concentrations and cognition outcomes in Alzheimer's disease patients: A multicenter, randomized, controlled clinical trial. *Journal of Alzheimer's Disease*, 2017;56(1):129-143. doi: 10.3233/JAD-160565.

Caldwell, J., Gendreau, R.M., & Furst, D. (1999). A pilot study using a staph protein A column (Prosorba) to treat refractory rheumatoid arthritis. *Journal of Rheumatology, 26,* 1657-1662.

Cortese, I., Chaudhry, Y., et al. (2011). Evidence-based guidelines update: Plasmapheresis in neurologic disorders: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 76:294. Reaffirmed on January 23, 2016.

Diseases treated by TA [American Society for Apheresis guidelines] [On-line]. Retrieved from the World Wide Web June 19, 2002. Available: http://www.bamap.com/diseases_cat1.html

Diseases treated by TA [American Society for Apheresis guidelines] [On-line]. Retrieved from the World Wide Web August 3, 1999. Available: http://www.bamap.com/Cat-1.htm

Egan, L., Sandborn, W. (2005, December). Positioning novel biologic, probiotic, and apheresis therapies for Crohn's disease and ulcerative colitis. *Current Gastroenterology Reports*, 7(6):485-91.

Fukuda, Y., Matsui, T., Suzuki, Y., et al (2004, December). Adsorptive granulocyte and monocyte apheresis for refractory Chrohn's disease: an open multicenter prospective study. *Journal of Gastroenterology* 39(12):1158-64.

Gibbard, F.B. (1993). Plasma exchange for Refsum's disease. *Transfusion Science, 14*, 23-26.

Grauhan, O., Meuller, J., Baeyer, H., Fietze, E., Cohnert, T., Meyer, R. Pfitzman, R., Mansfield, H., Siniawski, H., Warneke, H., & Hetzer, R. (1998). Treatment of humoral rejection after heart transplantation. *Journal of Heart and Lung Transplant, 17,* 1184-1194.

Green, D.M., Ropper, A.H. (2001). Mild Guillain-Barre syndrome. *Archives of Neurology*. 58,1098-101.

Haupt, W., (2000, August). Recent advances of therapeutic apheresis in Guillain-Barre syndrome. *Therapeutic Apheresis*, 4(4):271-4.

Hayes Directory. (2006, April 2011, May-archived). Plasma Exchange for Multiple Sclerosis. Lansdale, PA: Hayes, Inc.

Hayes Technology Brief. (2016, April). Plasma Exchange for Treatment of Steroid-Refractory Transverse Myelitis. Lansdale, PA: Hayes, Inc.

Health Care Financing Administration. (1999, April 15). Apheresis (therapeutic pheresis). *Medicare Coverage Issues Manual,* 35-60 [On-line]. Retrieved April 2, 2001 from the World Wide Web: http://www.hcfa.gov/pubforms/06%5Fcim/ci35.htm#_1_67

Hidaka, T., & Suzuki, K. (1997). Efficacy of filtration leukocytapheresis on rheumatoid arthritis with vasculitis. *Therapeutic Apheresis, 1*, 212-214.

Hidaka, T., & Suzuki, K. (1997). The mechanism of the efficiency of leukocytapheresis on rheumatoid arthritis. *Therapeutic Apheresis, 1,* 215-218.

Hillard, L.M., Williams, B.F., Lounsbury, A.E., Howard, T.H. (1998). Erythrocytapheresis limits iron accumulation in chronically transfused sickle cell patients. *American Journal of Hematology, 59,* 28-35.

Ipe, T.S., Pham, H.P., Williams III, L.A. (2017, June). Critical updates in the 7th edition of the American Society for Apheresis guidelines. *Journal of Clinical Apheresis*, https://doi.org/10.1002/jca.21562|

Katz, V.L., Watson, W.J., Thorp, J.M., Hansen, W., & Bowes, W.A. (1992). Treatment of persistent postpartum HELLP syndrome with plasmapheresis. *American Journal of Perinatology, 9,* 120-122.

Kawamura, A., Saitoh, M., Yonekawa, M., Horie, T., Ohizumi, H., Tamaki, T., Kukita, K, Meguro, J. (1999). New technique of leukocytapheresis by the use of nonwoven polyester fiber filter for inflammatory bowel disease. Therapeutic Apheresis, 3(4), 334-7.

Kitagaichi, M., Kusaoi, M., Tsukahara, T., Murayama, G., Nemoto, T., Sekiya, F., … Takasaki, Y. (2016, October). Safety and efficacy of the leukocytapheresis procedure in eighty-five patients with rheumatoid arthritis. Transfus Apher Sci. 2016 Oct;55(2):225-232. doi: 10.1016/j.transci.2016.07.019. Epub 2016 Jul 21.

Kosaka, T., Sawada, K. Ohnishi, K., Egashira, A., Yamamura, M., Tanida, N., Satomi, M., & Shimoyama, T. (1999). Effect of leukocytapheresis therapy using a leukocyte removal filter in Crohn's disease. *Internal Medicine, 38,* 102-111.

Landi, D., De Rossi, N., Zagaglia, S., Scarpazza, C., Prosperini, L., Albanese, M., … Italian PML study group. (2017, March). No evidence of beneficial effects of plasmapheresis in natalizumab-associated PML. *Neurology*, 88(12):1144-1152. doi: 10.1212/WNL.0000000000003740. Epub 2017 Feb 22.

Lehmann, H., Hartung, H., Hetzel, G., et al (2006, August). Plasma exchange in neuroimmunological disorders: part 2. Treatment of neuromuscular disorders. *Archives of Neurology* 63(8):1066-71.

Mabuchi, H., Koizumi, J., Shimizu, M., Kajinami, K., Miyamoto, S., Ueda, K., & Takegoshi, T. Long-term efficacy of low-density lipoprotein apheresis on coronary heart disease in familial hypercholesterolemia. *American Journal of Cardiology, 82,* 1489-1495.

Motomura, M., Hamasaki, S., Nakane, S., Fukuda, T., Nakao, Y.K. (2000). Apheresis treatment in Lambert-Eaton myasthenic syndrome. *Therapeutic Apheresis*, 4(4), 287-90.

Muscular Dystrophy Association. *Facts about plasmapheresis* [On-line]. Retrieved April 2, 2001, from the World Wide Web: http://www.mdausa.org/publications/fa-plasmaph.html

National Institute of Neurological Disorders and Stroke-Guillain-Barre Syndrome Fact Sheet. (NIH Publication # 11-2902). Bethesda, MD: Author.

National Institute of Neurological Disorders and Stroke-Multiple Sclerosis: Hope Through Research. (NIH Publication # 12-75). Bethesda, MD: Author.

National Institute of Neurological Disorders and Stroke-Myasthenia Gravis Fact Sheet. (NIH Publication # 10-768) Bethesda, MD: Author.

National Institutes of Health (1986). *NIH consensus statement: The utility of therapeutic plasmapheresis for neurological disorders* [On-line]. Retrieved April 2, 2001 from the World Wide Web: http://text.nlm.nih.gov/nih/cdc/www/56txt.html#Head0

National Institute of Neurological Disorders and Stroke-NINDS Acute Disseminated Encephalomyelitis Information Page. Retrieved December 28, 2012 from the World Wide Web at: http://search2.google.cit.nih.gov/search?q=plasmapheresis&site=NINDS&client=NINDS_frontend&proxystylesheet=NINDS_frontend&output=xml_no_dtd&filter=0&getfields=*&proxyreload=1

National Institute of Neurological Disorders and Stroke-NINDS Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) Information Page. Retrieved December 28, 2012, from the World Wide Web at:

http://search2.google.cit.nih.gov/search?q=plasmapheresis&site=NINDS&client=NINDS_frontend&proxystylesheet=NINDS_frontend&output=xml_no_dtd&filter=0&getfields=*&proxyreload=1

National Institute of Neurological Disorders and Stroke-NINDS Guillain-Barre Syndrome Information Page. Retrieved December 28, 2012 from the World Wide Web at: http://search2.google.cit.nih.gov/search?q=plasmapheresis&site=NINDS&client=NINDS_frontend&proxystylesheet=NINDS_frontend&output=xml_no_dtd&filter=0&getfields=*&proxyreload=1

National Institute of Neurological Disorders and Stroke-NINDS Lambert-Eaton Myasthenic Syndrome Information Page. Retrieved December 28, 2012 from the World Wide Web at: http://search2.google.cit.nih.gov/search?q=plasmapheresis&site=NINDS&client=NINDS_frontend&proxystylesheet=NINDS_frontend&output=xml_no_dtd&filter=0&getfields=*&proxyreload=1

National Institute of Neurological Disorders and Stroke-NINDS Miller Fisher Syndrome Information Page. Retrieved December 28, 2012 from the World Wide Web at: http://search2.google.cit.nih.gov/search?q=plasmapheresis&site=NINDS&client=NINDS_frontend&proxystylesheet=NINDS_frontend&output=xml_no_dtd&filter=0&getfields=*&proxyreload=1

National Institute of Neurological Disorders and Stroke-NINDS Neuromyelitis Optica Information Page. Retrieved December 28, 2012 from the World Wide Web at: http://search2.google.cit.nih.gov/search?q=plasmapheresis&site=NINDS&client=NINDS_frontend&proxystylesheet=NINDS_frontend&output=xml_no_dtd&filter=0&getfields=*&proxyreload=1

National Institute of Neurological Disorders and Stroke (NINDS)-Neuromyelitis Optica Information page. National Institutes of Health, June 2019. https://www.ninds.nih.gov/Disorders/All-Disorders/Neuromyelitis-Optica-Information-Page

National Institute of Neurological Disorders and Stroke-NINDS Paraneoplastic Syndromes Information Page. Retrieved December 28, 2012, from the World Wide Web at: http://search2.google.cit.nih.gov/search?q=plasmapheresis&site=NINDS&client=NINDS_frontend&proxystylesheet=NINDS_frontend&output=xml_no_dtd&filter=0&getfields=*&proxyreload=1

National Institute of Neurological Disorders and Stroke-NINDS Refsum Disease Information Page. (2011, September). Retrieved December 28, 2012 from the World Wide Web at: http://search2.google.cit.nih.gov/search?q=plasmapheresis&site=NINDS&client=NINDS_frontend&proxystylesheet=NINDS_frontend&output=xml_no_dtd&filter=0&getfields=*&proxyreload=1

National Institute for Neurological Disorders and Stroke. (1997). *Guillain-Barre fact sheet*. (NIH Publication No. 98-2902). Bethesda, MD: Author.

National Institutes of Health. (1996). Multiple Sclerosis: Hope through research [On-line]. Retrieved August 6, 1999, from the World Wide Web. Retrieved April 2, 2001, from the World Wide Web: http://www.ninds.nih.gov/health_and_medical/pubs/multiple_sclerosis.htm

National Institutes of Health. *Supplemental information for NIH consensus statement on the utility of therapeutic plasmapheresis for neurological disorders* [On-line]. Retrieved from the World Wide Web August 20, 1999. Available: http://odp.od.nih.gov/consensus/cons/056/056_supplement.htm

Pham, H.P., Schwartz. J. (2016, Nov). New apheresis indications in hematological disorders. *Current Opinion in Hematology*, 23(6):581-587.

Ronager, J., Ravnborg, M., Hermansen, I., Vorstrup, S. (2001). Immunoglobulin treatment versus plasma exchange in patients with chronic moderate to severe myasthenia gravis. Artificial Organs, 25(12), 967-73.

Sawada, K. Ohnishi, K., Kosaka, T., Chikano, S., Egashira, A., Izawa, H., Yamamura, M., Amano, K., Satomi, M., Shimoyama, T. (1997). Leukocytapheresis with leukocyte removal filter as a new therapy for ulcerative colitis. *Therapeutic Apheresis, 1,* 207-211.

Schwartz, J., Padmanabhan, A., Aqui, N., Balogun, R.A. Connelly-Smith, L. Delaney, M., ... Shaz, H. (2016). Guidelines on the use of therapeutic apheresis in clinical practice-evidence based approach from the Writing Committee of the American Society of Apheresis. The Seventh Special Issue. *Journal of Clinical Apheresis*, 31:149-338. doi:10.1002/jca.21470.

Scott, T., Frohman, E., De Seze, J., et al. (2011, December). Evidence-based guideline: clinical evaluation and treatment of transverse myelitis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology.* 77(24):2128-34.

Shehata, N., Kouroukis, C., Kelton, J. (2002, July). A review of randomized controlled trials using therapeutic apheresis. *Transfusion Medicine Reviews* 16(3):200-29.

Smith, J.W., Weinstein, R., Hillyer, K.L. (2003). Therapeutic Apheresis. Retrieved November 10, 2008 from the World Wide Web: http://www.clinlabnavigator.com/transfusion/therapeuticapheresis.html

Szczepiorkowski, Z., Winters, J., Bandarenko, N., et al. (2010). Guidelines on the use of therapeutic apheresis in clinical practice-evidence based approach from the Apheresis Applications Committee of the American Society for Apheresis. *J. Clin. Apher.* 25(3):83-177.

Turner, M.S., Sutton, D., Sauder, D.N. (2000). The use of plasmapheresis and immunosuppression in the treatment of pemphigus vulgaris. Journal of the American Academy of Dermatology, 43(6), 1058-64.

Up To Date. (2018, July). Therapeutic apheresis (plasma exchange or cytapheresis): Indications and technology. Authors: Fridey, J.L., Kaplan, A.A.

UptoDate. (2019, June). Progressive multifocal leukoencephalopathy: Treatment and prognosis. Author: Koralnik, I.J.

Zeiler, F.A., Matuszczak, M., Teitelbaum, J.; Kazina, C.J., Gillman, L.M. (2016, Dec). Plasmapheresis for refractory status epilepticus, part I: A scoping systematic review of adult literature. *Seizure*. 43:14-22. doi: 10.1016/j.seizure.2016.10.012. Epub 2016 Oct 19. DOI: 10.1016/j.seizure.2016.10.012

Zeiler, F.A., Matuszczak, M., Teitelbaum, J., Kazina, C.J., Gillman, L.M. (2016 Dec). Plasmapheresis for refractory status epilepticus Part II: A scoping systematic review of the pediatric literature. *Seizure,*43:61-68. doi: 10.1016/j.seizure.2016.11.010. Epub 2016 Nov 19. DOI: 10.1016/j.seizure.2016.11.010